PCT/US99/17222

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

HALEY, James, F., Jr.
Fish & Neave
1251 Avenue of the Americas
New York, NY 10020
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 02 November 2000 (02.11.00)	
Applicant's or agent's file reference STK/070 PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US99/17222	**International filing date** (day/month/year) 30 July 1999 (30.07.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
VUKICEVIC, Slobodan Dvorniciceva 7 Zagreb Croatia	HR	HR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
VUKICEVIC, Slobodan Jurjevska 62 10000 Zagreb Croatia		
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Leitao
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
FISH & NEAVE
Attn. Li, Z. Ying
1251 Avenue of the Americas
New York, NY 10020
UNITED STATES OF AMERICA

RECEIVED
FEB 23 2000
FISH & NEAVE - PATENT DEPT.
REFERRED TO
NOTED BY

Applicant's or agent's file reference STK/070 PCT	Date of mailing (day/month/year) 14/02/2000
International application No. PCT/US 99/17222	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant STRYKER CORPORATION et al.	International filing date (day/month/year) 30/07/1999

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

DOCKETED FOR April 14, 2000

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Nina Vercio

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

1/5/01

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Sieberstrasse 4
D-81675 München
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
29. Dez. 2000
First
Board

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28.12.2000
Applicant's or agent's file reference E 1645 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17222	30/07/1999	06/10/1998

Applicant
STRYKER CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

EK708046461US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
E 1645 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17222	30/07/1999	06/10/1998
International Patent Classification (IPC) or national classification and IPC A61K38/18		
Applicant STRYKER CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheet.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/04/2000	28.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/17222

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-42	as originally filed				
Claims, No.:					
1-46,48-50, 52-56	as originally filed				
47,51	as received on	10/11/2000	with letter of	09/11/2000	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-34 and 47-56 (industrial applicability).

because:

   ☒ the said international application, or the said claims Nos. 1-34 and 47-56 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-6, 12-13, 17-24, 26, 28-34, 37-39, 41-46 and 49-56
	No:	Claims	1-4, 7-11, 14-16, 25, 27, 35-36, 40, 47 and 48
Inventive step (IS)	Yes:	Claims	-

	No:	Claims	1-56
Industrial applicability (IA)	Yes:	Claims	35-46 (1-34 and 47-56 see separate sheet)
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Claims 1-34 and 47-56 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2- Reference is made to the following documents:

D1: WO 96 14335 A (US HEALTH ;LUYTEN FRANK P (US); MOOS MALCOLM JR (US); CHANG STEVEN) 17 May 1996 (1996-05-17)

D2: WO 98 31788 A (GENETICS INST) 23 July 1998 (1998-07-23)

D3: WO 95 16035 A (GENETICS INST ;HARVARD COLLEGE (US)) 15 June 1995 (1995-06-15)

D4: WO 95 33502 A (CREATIVE BIOMOLECULES INC) 14 December 1995 (1995-12-14)

D5: WO 96 39170 A (GENETICS INST) 12 December 1996 (1996-12-12)

D6: CUI P C ET AL: 'Repair of thyroid cartilage defect with bone morphogenetic protein.' ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, (1997 APR) 106 (4) 326-8. , XP000867788

D7: VUKICEVIC S (REPRINT) ET AL: 'Thyroid and articular cartilage repair in dog and sheep by OP -1' BONE, (APR 1999) VOL. 24, NO. 4, page 57 XP000867793

D8: MAJSTOROVIC L (REPRINT) ET AL: 'Biological repair of thyroid cartilage defects by osteogenic protein-1 (bone morphogenetic protein-7) in dog' BONE, (APR 1999) VOL. 24, NO. 4, page 42 XP000867794

NOVELTY - Art. 33 (1) and (2) PCT

3- Claims 1-4, 7-11, 14-16, 25, 27, 35-36, 40, 47 and 48 are not novel for the following reasons:

3.1- D1 discloses (e. g. p 3 lines 4-22 and p 4 lines 21-36) cartilage-derived morphogenic proteins having in vivo chondrogenic activity (CDMP-1 (GDF-5 or MP-52) and CDMP-2 (GDF-6)) in combination with a matrix (e. g. freeze dried cartilage, collagen, hydroxyapatite, polylactic acid, polyethylene glycol) for the repair (cartilage formation - see e. g. p 2 lines 10-11, p 3 lines 4-23, and p 4 lines 21-36) of cartilage (e. g. subglottic stenosis, tracheomalacia, chondromalacia patellae, osteoarthritis, joint surface lesions).

Hence, D1 relates to the repair/formation of articular and also non-articular cartilage (which is implicitly functional).

As mentioned in D1, the CDMPs can be combined with any of a number of suitable carriers. An appropriate carrier can be selected from the group comprising fibrin glue, cartilage grafts, and collagens (p 19 lines 17-29).

Therefore, in the light of D1, claims 1-4, 7-11, 14-16, 25, 27, 35-36, 40, 47 and 48 lack novelty.

3.2- The composition of D3 which is used for tendon/ligament-like tissue healing and tissue repair differs from that of the present application in that it comprises BMP-12 or BMP-13 alone or in combination with other BMPs. Hence, amended claim 51, and its dependent claims appear to be formally novel over D3.

3.3- D5 discloses the use of osteogenic proteins for the repair/healing of cartilaginous tissue (e. g. articular cartilage, meniscus) and osteoarthritis but does not explicitly mention the repair/healing of non-articular cartilage. Hence, D5 does not formally destroy the novelty of claims 1, 6, 14, 18-20, 24-29, 33 and 34. However, it is to be noted that a compound/device is only defined by its components and not by its

intended use, and therefore, claims 40 and 43 lack novelty in the light of D5.

D5 describes methods for inducing cartilaginous tissue formation in a patient in need of same comprising administering to said patient an effective amount of a composition comprising a protein which exhibits the abiiity to induce formation of cartilaginous tissue, such as BMP-13, BMP-12 and MP-52 (i. e. GDF-5).

The above mentioned compositions of D5 may include an appropriate matrix and/or sequestering agent as a carrier. Preferred matrices include collagen-based materials, including sponges or collagen in an injectable form, as well as sequestering agents, which may be biodegradable, for example hyaluronic acid derived. Biodegradable materials, such as cellulose films, or surgical meshes, may also serve as matrices. Such materials could be sutured into an injury site, or wrapped around the cartilage. Another preferred class of carrier are polymeric matrices, including polymers of poly(lactic acid), poly(glycolic acid) and copolymers of lactic acid and glycolic acid. These matrices may be in the form of a sponge, or in the form of porous particles, and may also include a sequestering agent. Preferred families of sequestering agents include blood, fibrin clot and/or cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol).

3.4- D6 discloses the administration of bBMPs for replacing lost laryngotracheal cartilage and reports the resulting new bone formation (cartilage was initially formed but eventually gave room to new bone). D6 differs from the present application in that the replacement tissue which is formed is not functional cartilage, but bone. Hence, D6 does not destroy the novelty of claims 1, 3, 4, 8 and 34.

3.5- Claims 5-6, 12-13, 17-24, 26, 28-34, 37-39, 41-46 and 49-56 appear to be formally novel over the available prior art.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

4- The problem posed in the present application is to provide means for inducing in vivo formation of functional replacement nonarticular cartilages and ligament tissues.

4.1- The solution proposed is the administration of an osteogenic protein in a biocompatible, bioresorbable carrier.

4.2- D1 discloses a method of stimulating (articular and non-articular) cartilage formation in a mammal by supplying cartilage-derived morphogenic proteins (i. e. osteogenic proteins) in a biocompatible, bioresorbable carrier.

Therefore, D1 is the closest prior art.

5- Claims 1-56 lack inventive step for the reasons stated below:

5.1- Claims 1-11, 14-16, 25, 27, 35-36, 38, 40, 46, 47 and 48 which are not novel, are also not inventive.

5.2- D2 discloses osteogenic proteins (e. g. OP-1, BMP-2) in combination with a carrier (e. g. collagen, demineralized bone matrix, blood, alkylcellulose, carboxymethylcellulose, hydroxyapatite, oloxamer, polylactides, PEG) for the repair of osteoporotic bones, osseous defects, cartilage defects, tendons and ligaments (see p 4 line 9 - p 5 line 25, p 6 line 18- p 7 line 22 and p 9 line 19 - p 10 line 19).

D2 discloses alternative BMPs and carriers to those of D1 and mentions the repair of tendons and ligaments, and hence, the teachings of D1, combined with those of D2, anticipate the subject matter of claims 1-4, 7-11, 14-16, 19-22, 25-31, 35-50 and said claims lack inventive step.

5.3- Provided the teachings of D3 (see item 4.2- above), it would be obvious for the person skilled in the art to provide an osteogenic protein other than and equivalent to BMP-12 and/or BMP-13 in a biocompatible, bioresorbable carrier to the larynx (defect locus), thereby inducing the formation of functiona! replacement ligament tissue in said larynx wherein the carrier comprises cartilage (as seen in e. g. D4) and the osteogenic protein is OP-1 (as seen in e. g. D2).

Therefore, claims 51-56 lack inventive step.

[D4 encloses devitalized matrices(e. g. cartilage, ligament, tendon, collagen, hydroxyapatite) in combination with osteogenic protein (e. g. OP-1, OP-2) and eventually binding material (e. g. carboxymethylcellulose) for replacement of body part or tissue (articular cartilage, ligament, tendon in skeletal joint)].

5.4- The features "intervertebral disc" and "interarticular meniscus" (claims 5-6, 12-13, 17-18, 23-24 and 32-33) are merely two of several non-articular cartilages and are equivalent to the features of e. g. claims 1-4 (note that the repair of meniscus (interarticular is not mentioned) is also disclosed in D5).

Hence, claims 5-6, 12-13, 17-18, 23-24 and 32-33 lack inventive step.

5.5- The perichondrium is the fibrous membrane of connective tissue covering the surface of cartilage (note that fibrocartilage has no perichondrium). It would be therefore obvious for the skilled man to implant the osteogenic protein and the carrier under the perichondrium of the non articular cartilage tissue for the purpose of the present application.

Thus, claim 34 lacks inventive step.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

6- For the assessment of the present claims 1-34 and 47-56 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6.1- Claims 35-46 appear to be industrially applicable.

Re Item VIII
Certain observations on the international application

7- Note that claim 45 is missing from amended page 48 (original claim 45 has been examined).

8- There is an inconsistency within claim 34 since fibrocartilage (non-articular cartilage) has no perichondrium (Art. 6 PCT).

46. The device of claim 43, wherein the carrier further comprises allogenic or autologous blood.

47. A method of promoting chondrogenesis at a nonarticular defect locus in a mammal, the method comprising providing an osteogenic protein in a devitalized cartilage carrier to the defect locus, wherein the cartilage carrier is configured to fit into the defect locus

48. The method of claim 47, wherein the cartilage carrier is a cartilage allograft.

49. The method of 47, wherein the osteogenic protein comprises an amino acid sequence having at least 70% homology to the C-terminal 102-106 amino acids, including the conserved seven-cysteine domain, of human OP-1.

50. The method of claim 49, wherein the osteogenic protein is human OP-1.

51. A method of repairing a defect locus in a ligament in a mammal, the method comprising providing an osteogenic protein in a biocompatible, bioresorbable carrier to the defect locus, thereby inducing the formation of functional replacement ligament tissue, wherein said osteogenic protein is not BMP-12 or BMP-13, and said defect locus is not in a skeletal joint.

52. The method of claim 51, wherein the defect locus is in the larynx.

53. The method of claim 51, wherein the carrier comprises cartilage.

IN THE EUROPEAN PATENT OFFICE
BEFORE THE INTERNATIONAL SEARCHING AUTHORITY

Atty. Docket No: STK-070 PCT

In re International Application: STRYKER CORPORATION *et al.*

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For: REPAIR OF LARYNX, TRACHEA, AND OTHER FIBROCARTILAGINOUS TISSUES

European Patent Office
Storage and Retrieval of Amino
Acid and Nucleotide Data
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STATEMENT ACCOMPANYING SEQUENCE LISTING

Dear Sir:

The undersigned hereby states that the Sequence Listing submitted concurrently herewith does not include matter which goes beyond the content of the application as filed and that the information recorded on the diskette submitted concurrently herewith is identical to the written Sequence Listing.

Respectfully submitted,

Nov. 24, 1999
Date

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